Effect of ipratropium bromide and/or sodium cromoglycate pretreatment on water-induced bronchoconstriction in asthma

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Effect of ipratropium bromide and/or sodium cromoglycate pretreatment on water-induced bronchoconstriction in asthma. C.M.E. Tranfa, A. Vatrella, R. Parrella, F. Bariffi. ©ERS Journals Ltd 1995.

ABSTRACT: The mechanisms underlying water-induced bronchoconstriction are still not fully understood. Cholinergic reflexes and mast cell mediator release are currently believed to play an important pathogenetic role.

In order to evaluate the relative contribution of each of these mechanisms, we studied the effect of ipratropium bromide (80 µg), a muscarinic antagonist, and sodium cromoglycate (20 mg), an inhibitor of mast cell mediator release, administered alone and in combination, in the prevention of bronchospasm induced by ultrasonic mist of distilled water (UMDW). Fifteen patients with documented atopic asthma and hyperresponsiveness to distilled water were selected for this randomized, placebo-controlled, double-blind study. Airway responses to pharmachological agents and bronchial challenge were measured by change in specific airways conductance (sGaw).

Sodium cromoglycate had no effect on bronchial calibre, whilst ipratropium bromide and the combination of the two drugs produced a significant bronchodilation 30, 60 and 90 min after treatments. The maximal increase in sGaw (mean %±SD) was observed at 90 min: 63±28% and 58±22% after ipratropium bromide and the combined drugs respectively. UMDW (2, 4, 8, 16 ml water) caused a -36±19%, -42±19%, -49±18%, -56±15% mean %±SD fall in sGaw after placebo. Pretreatment with sodium cromoglycate abolished the bronchoconstriction to 2 ml (fall sGaw -5±23% NS) and significantly reduced the effect of 4 (-15±22%), 8 (-21±20%) and 16 ml (-24±18%) water. Ipratropium bromide caused a weaker but significant attenuation; fall in sGaw was -15±15%, -18±19%, -30±21% and -41±27% with 2, 4, 8 and 16 ml water respectively. Treatment with both drugs prevented UMDW bronchoconstriction; a decrease in sGaw greater than 10% was observed in four subjects only.

These results suggest that water-induced bronchoconstriction is determined by more than one mechanism.
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It is well-known that both hypotonic and hypertonic saline aerosols cause cough and bronchoconstriction in asthmatic subjects [1, 2]. Current evidence indicates that the alteration in osmolarity away from iso-osmolarity of inhaled solutions is the stimulus for bronchospasm, whilst cough may be induced by the absence of a permeant anion in the aerosols, even if produced with iso-osmolar solutions [3]. Inhalation of ultrasonic mist of distilled water (UMDW) alters the osmolarity of the periciliary fluid lining [4]. There are a number of possible mechanisms by which osmotic changes may induce bronchoconstriction. These include: 1) alterations in epithelial permeability and consequent activation of vagal reflexes [5]; 2) release of mast cell mediators [6, 7]; 3) stimulation of C-fibre endings and the consequent involvement of the noncholinergic excitatory system [8]. It has recently been hypothesized that stimuli producing osmotic changes of the airway surface liquid, and consequently

of the bronchial submucosa, cause an increase in airway blood flow [9]. It has still to be established whether the increase in blood flow contributes in any way to the airway narrowing that follows osmotic stimuli [10].

Sodium cromoglycate (SCG) is an anti-allergic drug, effective in inhibiting both early and late allergen-induced bronchoconstriction [11]. The ability of SCG to prevent the immediate response has been suggested to result from inhibition of mediator release by activated mast cells [12, 13]. Some studies, however, suggest that SCG may also act by different mechanisms in preventing asthma. It could block activation of C-fibre endings [14]; or antagonize platelet-activating factor (PAF)-induced bronchospasm and inflammation [15]; or inhibit protein kinase C activity [16]; this enzyme being involved in airway smooth muscle contraction.

Ipratropium bromide (IB), a synthetic derivative of atropine, is a cholinergic antagonist of muscarinic receptors.

It is an effective bronchodilator in asthma, and can antagonize vagally-mediated bronchoconstriction, whilst it has no effect on mast-cell mediator release [13].

Either SCG or IB, administered alone, exerts an incomplete protective effect against water-induced bronchoconstriction [2, 17]. This is probably due to the fact that each of these two drugs is able to block only some of the various mechanisms potentially responsible for the bronchoconstricting action of UMDW.

Therefore, we decided to investigate whether the association of an agent that is thought to inhibit mediator release and an agent that inhibits parasympathetic pathways might provide a better protective effect against inhalation of UMDW. With this aim, 15 patients with stable atopic asthma, hyperresponsive to UMDW, were challenged on four separate days after treatment with IB, SCG, both drugs, and placebo.

Methods

Subjects

Fifteen patients (8 females and 7 males) aged 16–43 yrs (mean±SD 27±10 yrs), with documented atopic asthma and hyperresponsiveness to UMDW, gave their informed consent to participate in this study. Patient characteristics on admission to the trial are summarized in table 1. All of the asthmatic subjects were symptom-free during the experiments, with a baseline forced expiratory volume in one second (FEV_1) not less than 75% of predicted value, and a reduction of at least 35% in specific airway conductance (sGaw) after increasing doses of UMDW. No patient received corticosteroids, antihistamines and anti-allergic drugs for at least a month before entry. Bronchodilating therapy was withheld for 24 h before the beginning of the study.

Protocol

Each of the 15 subjects was studied on four separate days between 9.00 and 12.00 a.m. On each day, after measurements of baseline respiratory function, the patients were treated according to the following randomized, double-blind experimental protocol: 1) IB: 80 µg (4 puffs) and SCG 20 mg (4 puffs); 2) IB and placebo (4 puffs); 3) placebo and SCG; 4) placebo and placebo.

IB and SCG (or their placebo) were administered, by metered-dose inhaler, 90 and 30 min before bronchial challenge, respectively. Respiratory function was evaluated at baseline, 30, 60 and 90 min after IB (or its placebo), and after each dose of distilled water.

Bronchial challenge

UMDW was generated by a De Vilbiss 65 ultrasonic nebulizer (De Vilbiss Co., Somerset, Pa, USA). This produces particles with a mass-median diameter of 4.7 µm [18]; the nebulizer was calibrated to spontaneously deliver 2 ml·min⁻¹. The water container was weighed before and after each challenge in order to measure the amount of distilled water that was nebulized during each challenge. However, the output delivered to the patient was likely to be reduced by the tubing used to connect the patient to the circuit [19]. Every subject inhaled UMDW through a mouthpiece with clipped nose by tidal breathing. On each day of study, every patient inhaled UMDW at 4 min intervals for 1, 1, 2 and 4 min (corresponding to 2, 2, 4, 8 ml of inhaled water, with cumulated doses of 2, 4, 8 and 16 ml, respectively).

Respiratory function

On each study day, indirect measurements of airway calibre were performed at baseline, 30, 60, 90 min after

Table 1. – Subject characteristics

Sub. No.	Age yrs	Sex	Height cm	Weight kg	FEV_1 % pred	sGaw cmH₂O⁻¹·s⁻¹	Allergy
1	26	F	170	67	87	0.142	G, C
2	43	F	162	59	83	0.084	HDM
3	18	F	181	76	81	0.080	G
4	16	F	163	71	85	0.106	HDM, G
5	22	F	160	64	83	0.110	HDM
6	22	M	181	78	88	0.101	HDM
7	19	M	173	85	87	0.108	HDM
8	41	M	168	77	100	0.159	HDM
9	39	F	170	72	83	0.088	G
10	18	M	180	78	96	0.122	HDM, G
11	21	M	181	74	84	0.088	HDM
12	20	M	174	82	90	0.100	G
13	30	F	154	45	88	0.106	G
14	35	F	159	65	81	0.136	HDM
15	40	M	173	71	75	0.110	G
Mean	27		169.9	70.9	86	0.109	
±SD	10		8.8	10	6.1	0.022	

Sub: subject; FEV_1: forced expiratory volume in one second; sGaw: specific airways conductance; % pred: percentage of predicted value; M: male; F: female; G: grass; C: cat; HDM: house dust mite.

administration of the 1st drug (or placebo), and 2 min after each dose of inhaled water. sGaw (cmH$_2$O$^{-1}\cdot$s^{-1}) was calculated from five pressure/flow and pressure/volume curves obtained with a whole-body, constant volume, pressure-compensated plethysmograph (Fenyves-Gut, Basel, Switzerland).

Statistics

Data were analysed by analysis of variance (ANOVA) and Student's t-test for paired data, at a significance level of p<0.05. Since prechallenge baseline values of sGaw after inhalation of IB and IB+SCG were significantly greater than those after placebo and SCG, we expressed the postchallenge values as percentage change with respect to prechallenge values.

Results

The baseline values for sGaw (cmH$_2$O$^{-1}\cdot$s^{-1}) were not significantly different on the four study days, with a mean±SD of 0.104±0.019 before the inhalation of placebo, 0.109±0.027 before SCG, 0.102±0.022 before IB, and 0.107±0.024 before SCG+IB. The drug-induced percentage changes in sGaw (mean±SEM) are shown in figure 1. Compared with the respective baseline values, SCG and placebo did not produce significant changes in sGaw, whilst IB alone and in association with SCG significantly modified bronchial calibre at 30, 60 and 90 min (p<0.001). The peak of bronchodilation was observed at 90 min after inhalation of IB; at this time, in most of the patients, sGaw increased more than 35% of baseline value.

Bronchial challenge-induced percentage changes in sGaw (mean±SEM), with respect to the prechallenge values,
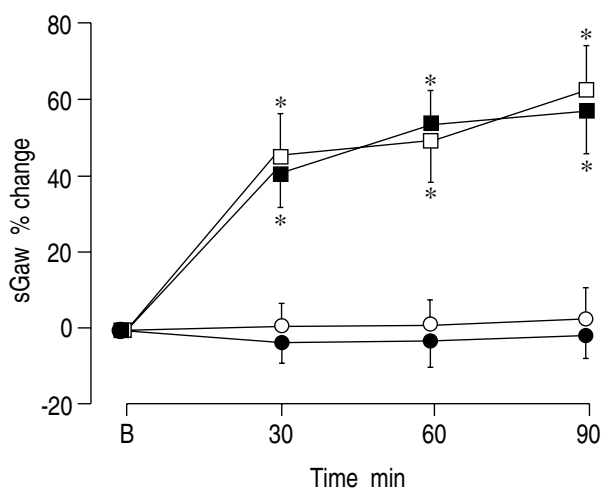

Fig. 1. – Percentage change in baseline sGaw (mean±SEM) in 15 asthmatics, after inhaling placebo (—●—), SCG (—○—), IB (—□—), and SCG+IB (—■—). B: baseline; sGaw: specific airways conductance; SCG: sodium cromoglycate; IB: ipratropium bromide. *: p<0.001 compared with baseline.
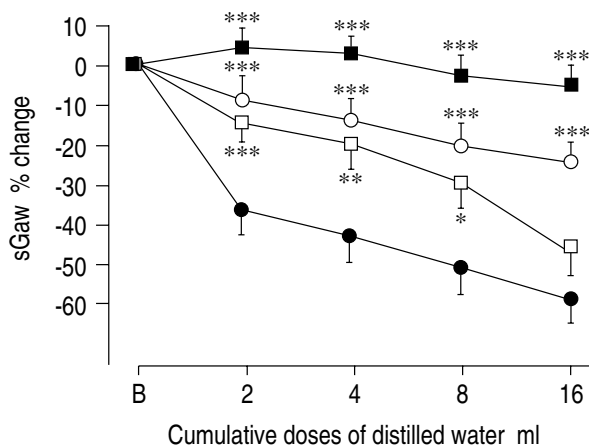

Fig. 2. – Effects of increasing doses of distilled water on airway calibre after treatment with placebo (—●—), SCG (—○—), IB (—□—) and SCG+IB (—■—). B: baseline sGaw 90 min after different treatments. Data represent mean±SEM of 15 asthmatics. For further abbreviations see legend to figure 1. *: p<0.02; **: p<0.01; ***: p<0.001 compared with placebo.
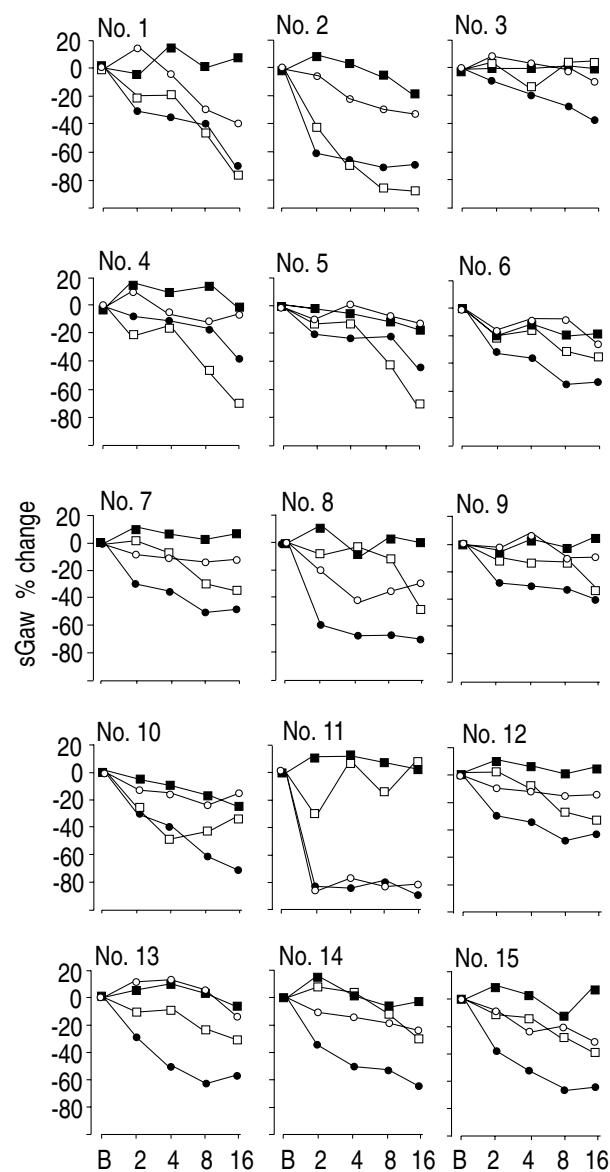

Fig. 3. – UMDW dose/response curves for each of 15 subjects after treatment with placebo (—●—), SCG (—○—), IB (—□—), and SCG+IB (—■—). B: baseline sGaw 90 min after different treatments. For further abbreviations see legend to figure 1.

are shown in figure 2. Dose-response curves for each of the 15 subjects are depicted in figure 3. Intragroup analysis showed that placebo did not affect bronchial response to inhaled water; in any of the tested subjects, a decrease in sGaw greater than 35% was observed. SCG partially blocked water-induced asthma; indeed, the whole group was protected only after inhaling the first dose of water (2 ml), whilst a significant decrease in sGaw was observed after the other three doses, with p-values <0.02, <0.01 and <0.001 after 4, 8 and 16 ml, respectively. However, in only two subjects (Nos. 1 and 11) the decrease in sGaw was greater than 35% of baseline values after completing the challenge. After IB pretreatment, all doses of inhaled water produced a statistically significant decrease in bronchial calibre (p<0.02 after 2 ml, p<0.01 after 4 ml and p<0.001 both after 8 and 16 ml).

In only six patients (Nos. 3, 9, 10, 11, 13 and 14) sGaw decreased by less than 35% compared with prechallenge values. Combined drugs significantly inhibited water-induced bronchospasm (fig. 2); the bronchoconstrictive response was completely prevented in 11 subjects and strongly attenuated in 4 (Nos. 2, 5, 6, 10) (fig. 3).

Statistical analysis of the differences observed between the protective effect of the distinct treatments revealed that SCG exerted a significantly greater effect than placebo: p<0.001 after 2, 4, 8 and 16 ml of inhaled water. IB produced similar results at lower doses (p<0.001 after 2 ml); however, it was less effective after 4 (p<0.01) and 8 ml (p<0.02), and at the end of the challenge its effect was not significant compared to placebo. No significant difference between SCG and IB action was detected. Compared with placebo, the combined drugs provided a significant protective effect after all doses of water (p<0.001). The combination of the two drugs exerted a greater effect than SCG (p<0.02 after 4 and 8 ml; p<0.01 after 16 ml) or IB alone (p<0.001 after all doses of water).

Discussion

The results of this study show that the IB+SCG association inhibits the bronchoconstriction caused by inhalation of distilled water in subjects with asthma. The combination of the two drugs provided a significantly better protection than either drug administered alone. Indeed, sGaw reduction was prevented in all of the 15 subjects even at the highest doses of inhaled water (16 ml); a decrease in sGaw greater than 10% was observed in only four patients.

Ipratropium bromide, at the dose used, provoked a significant bronchodilation, whilst it exerted an incomplete and variable protective effect, mainly at the highest doses of inhaled water. This behaviour suggests that activation of vagal reflexes does not represent the only mechanism involved in the pathogenesis of UMDW induced bronchoconstriction. Similar results were obtained by ALLEGRA and BIANCO [2]. A further reason for the poor action of IB in the prevention of water-induced asthma could be the lack of selectivity of IB towards muscarinic receptor subtypes. Indeed, IB also blocks the

M_2 subtype, located on postganglionic parasympathetic fibre endings, whose activation causes a negative feed back leading to a decrease in release of acetylcholine [20].

In comparison with IB, SCG attenuated UMDW induced bronchoconstriction in a greater number of subjects, thus providing a good protection against this bronchial challenge. However, as reported previously, SCG action was not significantly different from that of the antimuscarinic drug. The wide variation in the response observed among subjects might explain this result. In fact, dose-response curves show a large variability in the protective effect of either IB or SCG when used alone. The reason for this variability is not clear; it may be due to the relative importance of vagal mechanisms and mediator release in individual subjects. This hypothesis is supported by the marked protective effect exerted by the two drugs in combination.

In the present study, we observed a significant increase in bronchial calibre after administration of the antimuscarinic drug alone or in combination with SCG. This occurred despite the near normal baseline airway calibre of the selected patients. The bronchodilating effect of IB can complicate the interpretation of its protective efficacy. However, no correlation was observed between the degree of bronchodilation and the effect of IB on UMDW induced bronchoconstriction. A significant influence of bronchial calibre on airway reactivity is, therefore, unlikely. Previous studies have shown that the protective effect of antimuscarinic drugs on the bronchoconstriction caused by distilled water [21], or by other stimuli [22, 23], is not merely due to their effect on airway calibre.

In conclusion, the protective effect exerted by IB and SCG in combination suggests that more than one mechanism may be responsible for water-induced bronchospasm. It is likely that ipratropium bromide provides protection by inhibiting vagal efferent pathways, whilst cromolyn can inhibit mast cell mediator release. However, the wide individual variability observed in our study, and the uncertainty still surrounding the mechanism of action of cromolyn, make it impossible to precisely define the specific contribution of each of the distinct hypothesized mechanisms involved in water-induced bronchoconstriction.

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